IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	)	Group Art Unit: 1645
McKENZIE et al.	)	Examiner: Zeman, R.
Serial No.: 09/163,089	)	
Filed: September 29, 1998	)	DECLARATION OF DR. CHRISTOPHER W. SCHMIDT (Under 37 CFR 1.132)
Atty. File No.: 5036-1	)	
For: COMPOSITIONS FOR IMMUNOTHERAPY AND USES THEREOF	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Christopher W. Schmidt, declare as follows:

1. I am the Head of the Cancer Immunotherapy Laboratory and a Senior Research Officer at Queensland Institute of Medical Research (QIMR), Brisbane, Australia, and I am an expert in the fields of immunology and cancer immunotherapy. I am an Australian citizen and I currently reside in Australia. My curriculum vitae is attached to this declaration, which provides evidence of my extensive experience in the fields of immunology and cancer immunotherapy.

2. I have been engaged as an independent third party expert by PrimaBioMed Limited, of Victoria, Australia, which is the licensee of the above-identified application, to review the file of the above-identified application, and to provide my comments on certain issues in the prosecution of the application. I was compensated for my time on an hourly basis.

3. This Declaration is being submitted in conjunction with an Amendment and Response to an Office Action having a mailing date of August 12, 2005 in the above-identified application.

4. I have reviewed, and I am familiar with, the above-identified application and the presently pending claims, and I have also reviewed several documents from the file history of this application, including prior Declarations under 37 CFR 1.132 that were submitted by one of

the inventors, Dr. Geoffrey Pietersz, and the Office Action mailed August 12, 2005. The following discussion provides my comments on the Examiner's rejection of Claims 1, 3, 5-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. In particular, the following discussion addresses the Examiner's argument that the specification does not enable the use in the claimed composition of antigens other than MUC1 or CRIPTO, and that the specification allegedly provides no evidence which other conjugates would elicit the requisite immune response.

5. Comments on the Examiner's rejection

Introduction. Presentation of exogenous antigen by professional antigen presenting cells is crucial to the elicitation of effective cytotoxic T cell responses against non-haematopoietic infections and malignancies (1). The potential mechanisms of antigen uptake are endocytosis, macropinocytosis and phagocytosis. Of these, receptor mediated endocytosis or phagocytosis are the most efficient by 2-3 orders of magnitude. The presence of multiple mechanisms of receptor-mediated uptake (such as Fc, mannose and scavenger receptors), render the latter the most likely to function in cross presentation *in vivo*. The Transporter associated with Antigen Processing (TAP) transfers partially processed antigen from the cytosol into the endoplasmic reticulum. It is understood to be generally crucial for MHC Class I antigen presentation of endogenous antigens (4), and indeed its loss is common in tumours escaping immune surveillance (5). Although examples exist of direct loading of antigen fragments onto recycling MHC Class I molecules within endosomes, the TAP-dependence of exogenous antigen processing and presentation *in vivo* suggests that delivery of antigen into the cytosol is generally required for effective anti-tumour immunity (2), (3). It follows that efficient methods of introducing antigens into the cytosol are a critical step in anti-tumour vaccination.

Invention. The current claims relate to such a method. The inventors have demonstrated through working examples with specific antigens, that antigens linked to oxidised mannan (a carbohydrate polymer comprising mannose) generate efficient CD4 and CD8-mediated immunity. The presence of free aldehyde groups on the mannan is crucial for this enhanced efficiency compared to free antigen (6). These groups appear to allow egress from early endosomes into the cytosol. Given that the moiety possessing these groups is the mannan (rather than the antigen itself), it follows that this is a general method for delivering antigens into

the cytosol, and therefore allowing efficient cross presentation by professional antigen presenting cells. That the method has been successfully applied *in vivo* to antigens diverse as the tumour protein CRIPTO-1 (7), listeriolysin O, the heat shock protein Hsp65 of *Mycobacterium avium* (8), (9) as well as the much studied MUC1 antigen, supports the contention that the introduction of free aldehyde groups onto mannan prior to linkage to molecules in any form efficiently introduces the molecules into the cytoplasm, rendering antigens susceptible to proteasomal cleavage, transport into the endoplasmic reticulum, and loading onto MHC class I. Indeed, it has recently been shown that this same pathway may be used for MHC Class II presentation (10).

Pre-existing autoantibodies may divert the immune response induced by a vaccine (11). Pre-pulsing a professional antigen presenting cell such as a macrophage or dendritic cell *ex vivo* can bypass this problem, as demonstrated by data presented in the present application.

Enablement. The only variable that one might consider with regard to the use of the technology with a variety of antigens, is that for antigen conjugation to the mannose containing carbohydrate polymer. However, the method used is straightforward, textbook chemistry and is described in the application. The same method of conjugation used in the present application has been used subsequently for recombinant proteins, synthetic peptides, and to purified fractions of human tissue (12). It is therefore clear that the method described is indeed general in its application.

The synthesis or purification of tumour antigens of known sequence or biophysical characteristic is straightforward, and no particular complication in enablement arises from this generality.

The production of antigen presenting cells *ex vivo*, for example dendritic cells from monocyte precursors, is straightforward for cellular immunologists. My group produces such DC under GMP, i.e., a standard operating procedure is in place.

Feasibility of Generalization to other antigens. As noted in the background section of this declaration, the critical step in generating MHC class I-restricted T cell responses (and some MHC class II responses) is to effectively transport antigen into the cytosol. At the simplest level, for example, "hypertonic loading" has long been employed to introduce antigens into cells, allowing presentation through class I, albeit at the cost of damaging the cells (13). It is to be expected (and was known from prior to the date of filing) that a method that introduces antigen

into the cytosol, would therefore allow its presentation through MHC class I, and in some cases, MHC class II (based on more recent work). This makes no assumption that the loaded APC is the final, cross-presenting cell (14). Since the inventors have demonstrated that the free aldehyde groups in the invention allow access of endocytosed antigen into the cytosol, it is to be readily expected that the method would apply successfully to similarly conjugated proteins in general.

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6. I hereby declare that all statements made herein of my own are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

10 Feb 06 — Date

C Schmidt — Christopher W. Schmidt